REMARKS

Claims 14, 15, 19 and 21-36 are active in the present application. Support for Claims 28-36 is in the specification on page 1, lines 6-10, page 21, line 22 and page 22, line 14. No new matter is believed to be added by these amendments.

Applicants wish to thank Examiner Wilson for the courteous discussion granted to Applicants' undersigned U.S. representative on October 24, 2002.

Three primary issues were discussed on this date. The first was the rejection under 35 U.S.C. § 112, first paragraph (item 1 on page 3 of the Official Action). The Applicants' representative noted that the variable loop of HIV is well known and as a result the description of the 297 to 329 deletion one of skill in the art would know that this refers to an amino acid sequence deletion. As supporting evidence of this position, Applicants presented and now submit herewith a publication, Back et al,[1] which describes the gp41 coding region and the hypervariable region (see Figure 2). In light of the above-mentioned discussion and the attached evidence, withdrawal of the rejection of Claims 21, 24, 26, and 27 under 35 U.S.C. § 112, first paragraph is requested.

The next issue that was discussed centered on the description concerning how the V3 mutants were made, and particularly, in light of the rejection of Claims 14, 15, 19 and 21-27 under 35 U.S.C. § 112, first paragraph. The following serves to explain these mutants.

As described on page 26, lines 16-20, the vv-ΔV3 mutant with the Δ297-329 mutant was constructed from the pSVIII-env plasmid (obtained from J. Sodroski). As noted above the phrase Δ297-329 deletion with respect to the HIV V3 loop is clearly referencing the amino acid sequence of the glycoprotein.

In addition, it was known in the art at the time of filing the present application that the

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[1] *Journal of Virology* (1993) Vol.67 (11):6897-6902.

pSVIII-env plasmid with the Δ297-329 deletion from Dr. Sodroski's group also contained the insertion of three amino acids, Gly-Ala-Gly. In support of this position, Applicants refer the Examiner's attention to Wyatt et al[2], which is already of record, on page 6988, first column, section "Mutant envelope glycoproteins."

Concerning the 1ΔV3, WP and vvΔV3 mutants, please note the following. The issues dealing with the 297-329 mutant has been explained above. The constructs with the wildtype V3 clone from clone pIIIB to yield pSC-WTP (see page 27, lines 10-13). On page 27, line 12-13, the Applicants describe that the vv-ΔV3 and vv-WTP were generated using the wildtype (WT) and V3 mutant plasmids discussed above. Notwithstanding this description, the Examiner believes that the Applicants have failed to describe the mutants in Example 14. However, it appears the Examiner has not recognized that the constructs referred to in Example 14 are those constructed on page 27. Reading the Examples in their entirety clearly depicts that they are interconnected and cannot be read in as a stand-alone description, particularly, since the description of making the clones on page 27 uses the precise terminology that is used in the later testing examples, e.g., Example 14.

The last issue that was discussed concerned both the written description and enablement for the DNA constructs to be used as vaccines. The Examiner has taken the position that the specification coupled with the knowledge in the art does not support either written description or enablement of the vaccine claims. The Applicants' representative explained that when CTL, which are removed from an HIV infected individual, exhibit a strong response to a particular antigen *in vitro* (as is the case in the present application), this is strong evidence, that minimally, that antigen will be useful for priming the immune system in anticipation of an HIV infection. In addition, Applicants direct the Examiner's attention to

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[2]*Journal of Virology* (1992) vol. 66(12):6997-7004.

the attached publication of Rowland-Jones et al.[3] In this article, the importance of HIV-specific CTL in controlling viral levels during infection is discussed. CTL is not only important for the prevention of infection but for the continued progression of HIV infection to full blown AIDS. During the discussion noted above, the Applicants' representative also presented supporting evidence that the ΔV3 mutants described and claimed in the present application were effective for inducing a strong CTL response. This evidence is found in Kiska et al,[4] which is attached hereto. It is also noted that the inventors, Kozobor and Kaneko are also coauthors on the publication. The data presented in Kiska et al demonstrate that "vaccines expressing the ΔV3 mutant of either HIV-1_{IIIB} orHIV-$1_{89.6}$ envelope glycoproteins induced broader CD8+ T-cell activities than those elicited by the wildtype (WT) counterparts." (see the Abstract). Also on page 13, column 1, Kiska et al discuss why and how a CTL response is important to provide a vaccine against HIV infection. The present Inventors have discovered one way to provide that important CTL response, ie., using the ΔV3 mutants to elicit a strong and broad spectrum CTL response.

Concerning the claims that have been added in this amendment, i.e., Claims 28-36, are directed to, for example, a method of stimulating CTL activity, which is clearly shown by the Applicants in the specification and in the data identified in subsequent published work, i.e., Kmieciak et al and Kisaka et al.

Therefore, the specification taken with the knowledge in the field fully supports the fact that the present claims are adequately described and enabled under the meaning of 35 U.S.C. § 112, first paragraph. As a result, withdrawal of both rejections is requested.

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[3]*Immunology Letters* 66 (1999) 9-14.

[4]*Journal of Virology* (2002) vol. 76(9):4222-4232.

Applicants submit that the present application is now in a condition for allowance.

Early notification of such is earnestly solicited.

Respectfully submitted,

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IN THE SPECIFICATION

Page 26, replace the text beginning at line 12 with the following paragraph:

Page 26, replace the text beginning at line 12 with the following paragraph:

--The HIV-1IIIB isolate was the source of the full-length env gene and the ΔV3 loop mutant cloned in the pSCII-based vector under the control of a synthetic early/late vv promoter (Earl et al, 1990, Removal of cryptic poxvirus transcription termination signals from the human immunodeficiency virus type 1 envelope gene enhances expression and immunogenicity of a recombinant vaccinia virus. *J Virol. 64:2448-2451*). The vv-ΔV3 mutant with the Δ297-329 deletion[(15, incorporated by reference herein in its entirety)] was constructed by ligation of fragments obtained by PCR amplification from the pSVII-env plasmid (a gift from Dr. J. Sodroski, Dana-Farber Cancer Institute, Boston, MA). One fragment was generated by PCR with the synthetic oligonucleotide containing the *SalI* site and the CCACC Kozak's sequence in front of the ATG codon (5'-AGAGTCGACCCACCATGAGAGTGAAGGAGA-3', sense) (SEQ ID NO:1), and the oligonucleotide (5'-ACAGGTACCCCATAATAGACTGTGAC-3' antisense) (SEQ ID NO:2) containing the *Kpn*I side, used for ligation with the second env fragment. The second fragment was derived by *Kpn*I and *Bam*HI digests of the pSVIII-env plasmid, and the third fragment was generated by PCR with the synthetic oligonucleotide containing the *Bam*HI site at its 5' end (5'-AACGGATCCTTAGCACTTATCTGGG-3', sense) (SEQ ID NO:3) and the antisense primer (5'-TTGCGCGGCCGCTTATAGCAAAATCCTTTCC-3') (SEQ ID NO:4)

containing the TAA stop codon followed by the *Not*I site. The three fragments were ligated into the *Sal*I and *Not*I sites of the pSC11-based vector (a generous gift of Dr. L. Eisenlohr, Thomas Jefferson University, Philadelphia, PA) to generate plasmid pSC-ΔV3. A similar approach was used to generate plasmid with the WT env gene (pSC-WTP) using recombinant clone pIIIB (Hwang, et all, *Science* 253:71-74) kindly provided by Dr. B. Cullen (Howard Hughes Medical Institute, Duke University Medical Center, Durham, NC). Plasmids pSC-ΔV3 and pSC-WTP were used to generate vv-ΔV3 and vv-WTP by homologous recombination as described (Earl et al, 1990, *J Virol. 64:2448-2451*).--

IN THE CLAIMS

Claims 28-36 are added.